Bayer HealthCare
Consumer Care Division

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Bayer HealthCare LLC
Consumer Care Division
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910

August 1, 2005

Division of Dockets Management
5630 Fishers Lane Rm. 1061
Rockville, MD 20852

Re: **Docket No 1976N-0052N**
RIN 0910-AF34
Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Proposed Amendment of Monograph for Over-the-Counter Nasal Decongestant Products

Dear Sir or Madam,

In the November 2, 2004 Federal Register, the Food and Drug Administration (FDA) published and solicited comments on a proposed rule entitled "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Proposed Amendment of the monograph for Over-the-Counter Nasal Decongestant Products". The intention of the Proposed Rule was to add phenylephrine bitartrate as a generally recognized as safe and effective (GRASE) nasal decongestant when used in an effervescent tablet in combination with aspirin and chlorpheniramine maleate. Bayer HealthCare submitted comments to this proposed amendment on January 28, 2005.

As stated in the proposed Federal Register amendment, a pre-requisite to the addition of PEB to the FDA OTC Cough-Cold Monograph was its inclusion in the USP/NF Pharmacopeia. Attached please find an electronic printout of the USP 28 – NF 23 through Second Supplement official August 1, 2005 – December 31, 2005; the Phenylephrine bitartrate monograph has been included in the USP/NF and will be official August 1, 2005.

With the addition of phenylephrine bitartrate to the USP/NF on August 1, 2005, Bayer Healthcare is looking forward to its inclusion in the FDA monograph for Over-the-Counter Nasal Decongestant Products.

If you have any questions regarding the content of this letter, please contact the undersigned at 973-408-8181 or Bill Walsh at 973-408-8046.

Sincerely,

Linda Bowen

Linda F. Bowen
Associate Director, Regulatory Affairs
Bayer HealthCare LLC, Consumer Care Division

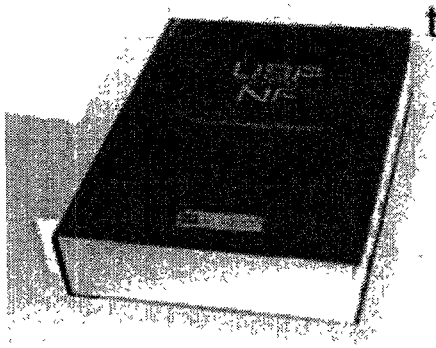
1976N-0052N

C 243

USP 28–NF 23

through *Second Supplement*

Official August 1, 2005 to December 31, 2005



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Add the following:

■**Phenylephrine Bitartrate**
$C_9H_{13}NO_2 \cdot C_4H_6O_6$ 317.3

R-2-(Methylamino)-1-(3-hydroxyphenyl)ethanol, hydrogen tartrate.

(–)-1-(3-Hydroxyphenyl)-2-methylaminoethanol, hydrogen tartrate.

(–)-3 Hydroxy-α-[(methylamino)methyl]benzenemethanol, hydrogen tartrate.

1-*m*-Hydroxy-α-[(methylamino)methyl]benzyl alcohol, hydrogen tartrate [*17162-39-0*].

» Phenylephrine Bitartrate contains not less than 99.0 percent and not more than 100.5 percent of $C_9H_{13}NO_2 \cdot C_4H_6O_6$, calculated on the dried basis.

Packaging and storage— Preserve in tight, light-resistant containers. Store at controlled room temperature.

USP Reference standards ⟨ 11 ⟩ — *USP Norphenylephrine Hydrochloride RS*. *USP Phenylephrine Hydrochloride RS*.

Identification—

A: *Infrared Absorption* ⟨ 197K ⟩.

B: The alkaline filtrate from the test for *Specific rotation* responds positively to the test for *Tartrate* ⟨ 191 ⟩.

Specific rotation ⟨ 781S ⟩**:** between –53° and –57° for the prepared sample.

Test solution— Prepare a sample solution of about 240 mg per mL in water. Make the solution slightly alkaline by adding concentrated ammonium hydroxide dropwise. Rub the wall of the vessel with a glass rod so that the base precipitates out. Filter the base under suction, wash with a little water and acetone, and dry at 105° for 2 hours. Prepare and measure a 50 mg per mL solution of base precipitate in 1 M hydrochloric acid.

pH ⟨ 791 ⟩**:** between 3.0 and 4.0 in 10% w/v aqueous solution.

Loss on drying ⟨ 731 ⟩— Dry at 105° to a constant weight: it loses not more than 0.5% of its weight.

Residue on ignition ⟨ 281 ⟩**:** not more than 0.1%.

Chromatographic purity—

Buffer solution— Dissolve 3.25 g of 1-octanesulfonic acid sodium salt monohydrate in 1 L of water. Adjust slowly with 3 M phosphoric acid to a pH of 2.8.

Solution A— Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (9:1).

Solution B— Prepare a filtered and degassed mixture of acetonitrile and *Buffer solution* (9:1).

Mobile Phase— Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨ 621 ⟩).

Diluent— Prepare a mixture of *Solution A* and *Solution B* (8:2).

System suitability solution— Dissolve accurately weighed quantities of *USP Phenylephrine Hydrochloride RS* and *USP Norphenylephrine Hydrochloride RS* in *Diluent,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about 1.0 mg per mL and 0.9 µg per mL, respectively.

Blank solution— Prepare a solution containing 0.8 mg per mL L(+)-tartaric acid in *Diluent*.

Test solution— Transfer 78 mg of Phenylephrine Bitartrate, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨ 621 ⟩)— The liquid chromatograph is equipped with a 215-nm detector and a 4-mm × 5.5-cm column that contains packing L1. The column and injection port temperatures are maintained at 45 ± 2°. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	93	7	equilibration
0–10	93→70	7→30	linear gradient
10–10.1	70→93	30→7	linear gradient
10.1–18	93	7	equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between norphenylephrine and (–)-phenylephrine is not less than 1.5; the tailing factor of (–)-phenylephrine is less than 1.8; and the relative standard deviation for replicate injections is not more than 5%.

Procedure— Separately inject equal volumes (about 4 µL) of the *Blank solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Phenylephrine Bitartrate taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the

peaks. [NOTE—Examine the chromatogram of the *Blank solution* for peaks and disregard any corresponding peaks observed in the chromatogram of the *Test solution.*] The limits of impurities are specified in the accompanying table.

Compound	Approximate Relative Retention Time	Limit (%)
Phenylephrine	1.0	—
Norphenylephrine	0.9	0.2
Phenylephrone	1.2	0.1
Benzylphenylephrine	2.9	0.2
Benzylphenylephrone	3.1	0.1
Individual unknown impurity	—	0.2
Total impurity	—	0.5

Assay— Transfer about 280 mg of Phenylephrine Bitartrate, accurately weighed, to a 100-mL beaker, and dissolve by stirring in 60 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid, determining the endpoint potentiometrically. Perform a blank determination (see *Titrimetry* ⟨ 541 ⟩), and make the necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 31.73 mg of $C_9H_{13}NO_2 \cdot C_4H_6O_6$. ■ *2S (USP28)*

Auxiliary Information— *Staff Liaison* : Daniel K. Bempong, Ph.D., Scientist
Expert Committee : (PA2) Pharmaceutical Analysis 2
USP28–NF23 Supplement : No. 2 Page 3520
Pharmacopeial Forum : Volume No. 31(3) Page 783
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